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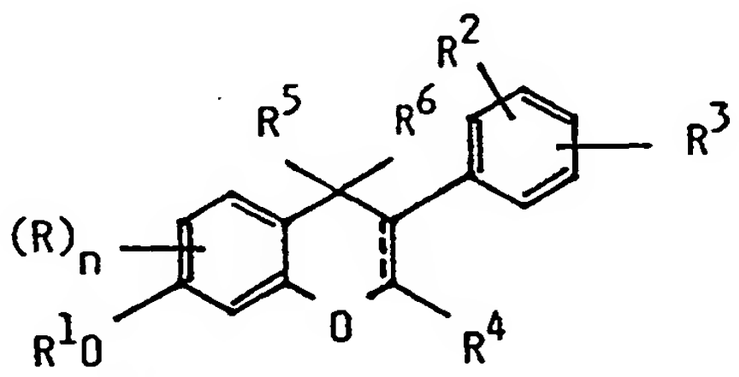
(54) Title: ISOFLAVONE DERIVATIVES

(57) Abstract

The present invention relates to isoflavone, isoflavan-4-one and isoflavane derivatives of general formula (I), their salts, pharmaceutical compositions containing the compounds of general formula (I), and to a process for preparing the same. In general formula (I), if n is 0, R^5 and R^6 together stand for an oxo group and the dotted line means a double bond, R^1 represents C_{1-18}alkyl substituted by alkylcarbonyl, carboxy, sulfonic acid, hydroxy, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N-(CH_2)_mCO(CH_2)_p-$ or by $(C_{1-4}alkyl)_2N-(CH_2)_mOCO(CH_2)_p-$ group; or stands for C_{3-6}cycloalkyl or cycloalkenyl; or if n is 1, R^5 and R^6 together stand for an oxo group and the dotted line means a double bond, R^1 represents C_{1-18}alkyl optionally substituted by alkyl-carbonyl, alkoxycarbonyl, carboxy, sulfonic acid, hydroxy, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N-(CH_2)_mCO(CH_2)_p-$ group; or stands for C_{3-6}-cycloalkyl or cycloalkenyl or C_{2-6}alkenyl; or if n is 0 or 1, R^5 and R^6 together stand for an oxo group or stand separately for hydrogen and the dotted line does not mean a chemical bond, R^1 represents C_{1-18}alkyl optionally substituted by alkyl-carbonyl, alkoxycarbonyl, carboxy, sulfonic acid, hydroxy, alkoxy, phenyl optionally substituted by a halo atom, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N-(CH_2)_mCO(CH_2)_p-$ group; or stands for C_{3-6}-cycloalkyl or C_{2-6}alkenyl; or R stands for C_{1-8}alkyl, halogen, C_{1-4}alkoxymethyl, C_{2-5}-acyloxymethyl, or hydroxymethyl; R^4 stands for hydrogen or C_{1-4}alkyl; R^2 and R^3 stand for hydrogen or C_{1-6}alkoxy; R^5 and R^6 together stand for an oxo group or separately stand for hydrogen; the dotted line means a double bond being optionally present; n is 0 or 1; m is an integer from 1 to 4; and p is an integer from 1 to 4. The compounds of general formula (I) can be used for the prevention and treatment of osteoporosis. They are prepared by methods well known in the organic chemistry.



(I)

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
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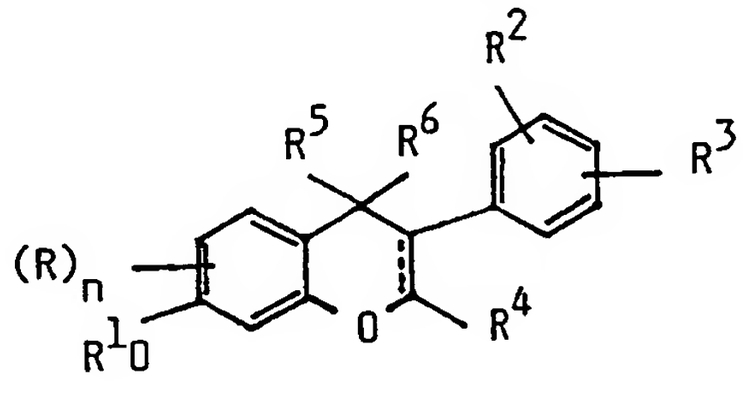
ISOFLAVONE DERIVATIVES

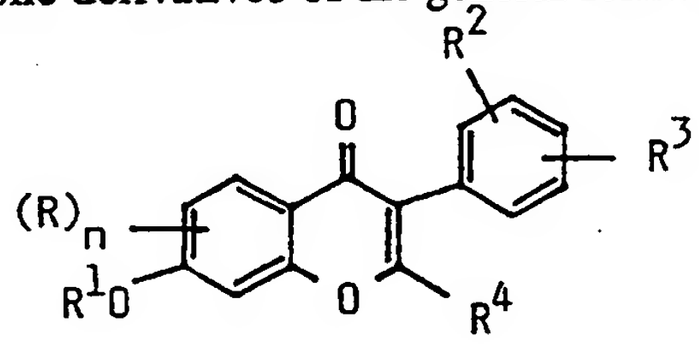
The present invention relates to isoflavone, isoflavan-4-one and isoflavane derivatives of the general formula (I),



(I),

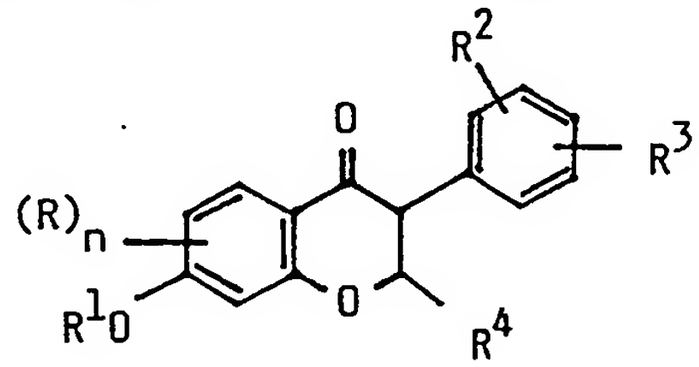
their salts, pharmaceutical compositions containing the compounds of the general formula (I), and to a process for preparing the same.

The isoflavone derivatives of the general formula



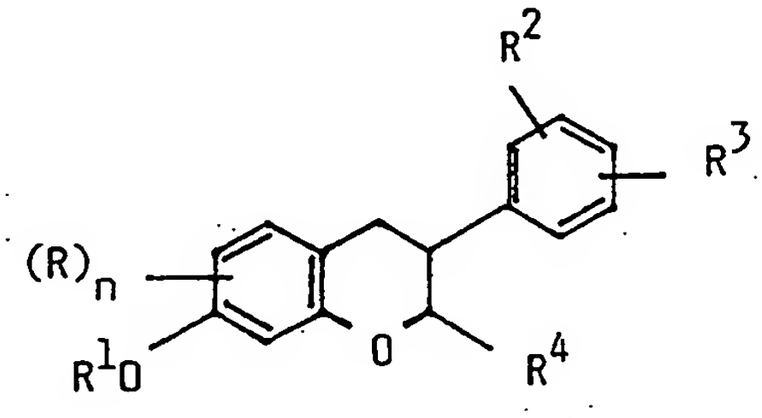
(IA),

the isoflavane-4-one derivatives of the general formula



(IB),

the isoflavane derivatives of the general formula



(IC)

form a narrower group of the compounds of the general formula (I).

In the general formula (I)

if n is 0, R^5 and R^6 together stand for an oxo group and the dotted line means a double bond,

R^1 represents C_{1-18}alkyl substituted by alkylcarbonyl, carboxy, sulfonic acid, hydroxy, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N\text{-}(CH_2)_mCO(CH_2)_p$- or by $(C_{1-4}alkyl)_2N\text{-}(CH_2)_mOCO(CH_2)_p$- group; or stands for C_{3-6}cycloalkyl or cycloalkenyl; or

if n is 1, R^5 and R^6 together stand for an oxo group and the dotted line means a double bond,

R^1 represents C_{1-18}alkyl optionally substituted by alkyl-carbonyl, alkoxycarbonyl, carboxy, sulfonic acid, hydroxy, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N\text{-}(CH_2)_mCO(CH_2)_p$- group; or stands for C_{3-6}-cycloalkyl or cycloalkenyl or C_{2-6}alkenyl; or

if n is 0 or 1, R^5 and R^6 together stand for an oxo group or stand separately for hydrogen and the dotted line does not mean a chemical bond,

R^1 represents C_{1-18}alkyl optionally substituted by alkyl-carbonyl, alkoxycarbonyl, carboxy, sulfonic acid, hydroxy, alkoxy, phenyl optionally substituted by a halo atom, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N\text{-}(CH_2)_mCO(CH_2)_p$- group; or stands for C_{3-6}-cycloalkyl or C_{2-6}alkenyl;

R stands for C_{1-8}alkyl, halogen, C_{1-4}alkoxymethyl, C_{2-5}-acyloxymethyl, or hydroxymethyl;

R^4 stands for hydrogen or C_{1-4}alkyl;

R^2 and R^3 stand for hydrogen or C_{1-6}alkoxy;

R^5 and R^6 together stand for an oxo group or separately stand for hydrogen; the dotted line means a double bond being optionally present;

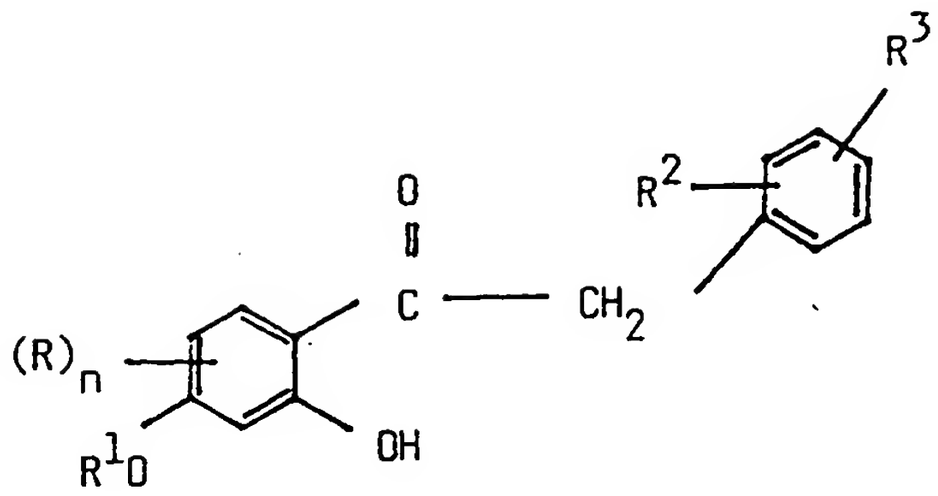
n is 0 or 1;

m is an integer from 1 to 4; and

p is an integer from 1 to 4.

The compounds of the general formula (I) can be used for the prevention and treatment of osteoporosis.

According to the invention the compounds of the general formula (IA) can be prepared by reacting ketones of the general formula



(III),

wherein R, n, R^1, R^2 and R^3 are as defined for the general formula (I),

a) with alkyl orthoformate in the presence of a basic catalyst, or

b) with hydrogen cyanide and/or cyanic salts in the presence of hydrohalides; or

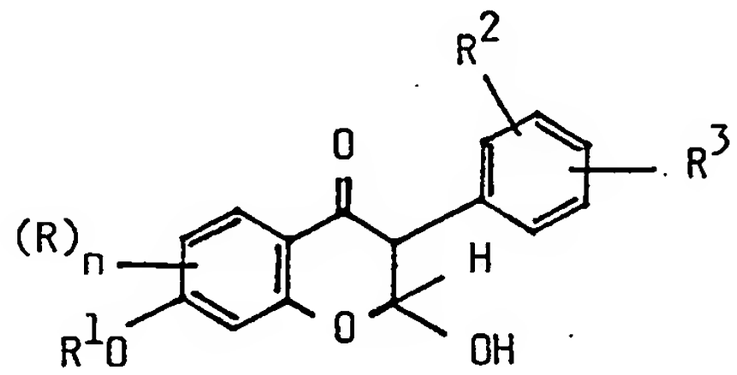
c) with alkyl formiate in the presence of an alkali metal; or

d) with alkyloxalylhalide, and the isoflavone ester thus obtained is, if desired, saponified and/or decarboxylated; or

e) with organic carboxylic anhydride; or

f) with N,N-dialkyl acid amide in the presence of phosphorous chloride; or

g) by dehydrating 2-hydroxy-isoflavanone derivatives of the general formula



(IV),

and if desired, converting an R^1 group into another R^1 group, or forming an R group in a compound of the general formula (I), wherein R stands for hydrogen, and, if desired, converting a compound of the general formula (I) thus obtained into its salt or setting it free from its salt.

According to process variant a) of the present invention a suitably substituted ketone is reacted with alkyl orthoformiate, preferably ethyl ester, in an aprotic solvent having a high boiling point. As a solvent pyrrolidine, dimethyl formamide or diethylene glycol dimethyl ether is used. As a basic catalyst preferably piperidine, morpholine, pyrrolidine and other secondary amines may be used.

According to process variant b) of the present invention the ketones are reacted with hydrogen cyanide in an aprotic solvent in the presence of dry gaseous hydrochloric acid or other hydrohalogenic acids or Lewis acids. Non-basic aprotic solvents may also be used in the reaction, preferably diethyl ether or other dialkyl ethers. As catalyst zinc chloride or other Lewis acids may be used.

The reaction is carried out with hydrogen cyanide or an appropriate salt thereof, preferably with zinc cyanide. The mixture may be saturated with dry gaseous hydrochloric acid and the substituted α-formimino-2-hydroxyphenylbenzyl-ketone chlorohydrates thus obtained are decomposed with aqueous treatment.

According to process variant c) of the present invention the ketones of the formula (III) are reacted with alkyl formiates in the presence of an alkali metal. One preferably proceeds by adding dropwise suitably substituted 2-hydroxyphenyl -benzyl-ketone dissolved in ethyl formiate onto pulverized metallic sodium, then by decomposing the reaction mixture with water and separating the isoflavone thus-obtained.

According to process variant d) of the present invention suitably substituted 2-hydroxy-phenyl benzyl ketones are reacted with alkyl oxalyl halides. A 2-alkoxycarbonyl-isoflavone derivative is obtained, which is, if desired, converted into an isoflavone derivative unsubstituted in position 2 by hydrolyzing the ester group and by subsequent decarboxylation. This process variant can preferably be carried out with methyl- or ethyl oxalyl chloride in the presence of a basic acid binding agent in an appropriate aprotic solvent, preferably pyridine or another tertiary amine.

According to process variant e) of the present invention the suitably substituted 2-hydroxy-phenyl benzyl ketone is reacted with organic acid anhydrides in the presence of a basic catalyst. As an organic acid anhydride acetic, propionic or benzoic anhydride can be used. The anhydride is heated in the presence of a basic catalyst, suitably an alkali salt of the acid component of the acid anhydride, or in the presence of tertiary amines, without solvent or in an aprotic solvent having high boiling point, such as pyridine or dimethyl formamide.

According to process variant f) of the present invention the ketone is reacted with N,N-dialkyl acid amides in the presence of phosphorus oxychloride, preferably by heating the suitably substituted 2-hydroxy-phenyl benzyl ketone with

N,N-dialkyl acid amid (e.g. dimethyl formamide or dimethyl acetamide) and phosphorous oxychloride, using as solvent the N,N-dialkyl acid amide itself.

According to process variant g) of the present invention 2-hydroxy-isoflavones of the formula (IV) are dehydrated by heating or by warming in an acidic medium in polar solvent.

In the first step of the process according to the invention such derivatives may be obtained from the compounds of the formula (III) or (IV) in which R^1 stands for hydrogen or it is not the R^1 group which is required in the target product.
In these cases the R^1 group is introduced into the place of the hydrogen atom or, respectively, an R^1 group is converted into another R^1 group.
This step can be carried out by the partial or total alkylation of the mono- or polyhydroxy-isoflavones, which alkylation can preferably be carried out by reacting with alkyl halides or substituted alkyl halides, alkyl sulfonic lactones, alkyl sulfates, olefines or epoxydes, preferably by heating the alkylating agent in a suitable solvent, e.g. ketones, dimethyl formamide or ethers containing a higher number of carbon atoms with the isoflavones to be alkylated. In case of halogens preferably an acid binding agent, such as alkali carbonate, and in case of alkyl bromides and alkyl chlorides preferably alkali iodide is present.
This step can be carried out by the partial or total desacylation or the partial and total desalkylation of acyloxy and polyacyloxy, alkyloxy and polyalkyloxy isoflavones. Acyloxy or polyacyloxy isoflavones are formed when process variant e) is carried out with di- or polyhydroxy phenyl benzyl ketones containing a hydroxy group in position 2. The desacylation is preferably carried out in an acidic or basic medium in the presence of a polar solvent. This step can also be carried out by decarboxylating isoflavone-2-carboxylic acids. Isoflavone-2-carboxylic acids are formed during process variant d) and their decarboxylation is preferably carried out by heating with or without the presence of a catalyst, such as copper dust.

The compounds of the general formula (IB), wherein R, n, R^1, R^2, R^3 and R^4 are as defined for general formula (I) are prepared by the reduction of the compounds of the general formula (IA), wherein R, n, R^1, R^2, R^3 and R^4 are as defined for general formula (I). The reduction is carried out by catalytic hydrogenation or by using metal hydrides.

In the case of the catalytic hydrogenation a nobel metal catalyst, preferably a palladium on charcoal catalyst is used and the reduction is carried out in an organic solvent, preferably in acetone.

As a complex metal hydride, preferably diisobutyl aluminum hydride is used and the reduction is carried out at a low temperature (-70 °C).
The compounds of the general formula (IC), wherein R, n, R^1, R^2, R^3 and R^4 are as defined for general formula (I) are prepared aby the catalytic hydrogenation of the compounds of the general formula (IB), wherein R, n, R^1, R^2, R^3 and R^4 are as defined for general formula (I), in the presence of a noble metal or nickel catalyst. The reduction is preferably carried out in a polar solvent, preferably acetic acid or ethyl acetate.

The compounds of the general formula (I), wherein R^1 stands for alkyl substituted by carboxy are prepared by hydrolysing the ester group of the compounds containing as R^1 an alkyl group substituted by alkoxycarbonyl. The hydrolysis is preferably carried out in an acidic medium, preferably with lower organic acids in the presence of a strong acid catalyst.

The compounds of the general formula (IA) containing a methyl group in position 6 are prepared by the reduction of halomethyl isoflavones obtained from the compounds of the general formula (IA) containing a hydrogen atom in position by halomethylation. The reduction is carried out preferably in the presence of metals, preferably zinc.

The compounds of the general formula (I) containing an alkoxy or hydroxymethyl group in position 6 are prepared either by replacing the halo atom of the halomethyl isoflavones prepared as described above with an alkoxy group by the aid of alcohols or by replacing said halo atom with an 0-acetyl group by the aid of sodium acetate and by subsequently converting the acetoxy group into an OH group.
We have found that the compounds of the general formula (I) and salts thereof can effectively be used for the prophylaxis and the treatment of osteoporosis.

It is known that Ipriflavone (7-Isopropoxy-isoflavone) is able to inhibit bone resorption either in vitro or in vivo (Notoya, K. et al. Inhibitory effect of Ipriflavone on pit formation in mouse unfractionated bone cells, Calcif.Tissue Int. 51, (Supl. 1) 53-56 (1992); Notoya, K. et al. Inhibitory effect of Ipriflavone on osteoclast-mediated bone resorption and new osteoclast formation in long-term

cultures of mouse unfractionated bone cells, Calcif Tissue Int. 50, 314-319 (1992). On the other hand, it is known that Ipriflavone also could increase the mineralization of the extracellular matrix of human bone cell cultures (Ref. Ecsedi, G.G. Model for in vitro investigation of bone mineralization, Agents and Actions 41, 84-85 (1994.)

To estimate the effectiveness of the compounds of the general Formula (I) on bone formation an in vitro mineralization model was developed. Under certain circumstances cultures of partially selected (osteoblast-enriched) human bone cells originated from either nasal bone of adults or foetus femur produce Type I collagene, bone specific proteins (e.g. osteocalcin), prostanoides (PGE2, PGF2α, PGI2, etc. and accumulate calcium into the synthesized matrix (Ref.: Ecsedi, G.G., Characterization of cells of human nasal bone cell cultures, 4th Int. Symposium on Osteoporosis, 27 March- 2 April, 1993 Hong Kong; Abstr. no. 534).
Method, Cells of subcultures 8-12 (usually 8th or 9th) were drop-inoculated at a density of 2*10^4 cells per well 96-well plates. On the day 3 the treatments were started with the compound of the Formula I at two concentrations, 10^-8 and 10^-10 M. Because ethanolic 10^-5 and 10^-7 M stock solutions of the compounds were used in the treatments all culture media contained 0.1 % ethanol including the Controls. Media were changed on each 2-3 day. The treatments were finished on the day 21, the total calcium (Ca) and DNA content of the 6-parallel samples were measured by Boehringer Test Combination (MPR3) and the spectrofluorometric 3,5-diaminobenzoic acid (DABA) method, respectively, then the ratios, Ca/DNA were calculated.

In the table of the compounds of Formula I below, data are given in percentages compared to the average of the Control value (100%)

Name of Compound	Concentration [-log M]	Ca %	DNA %	Ca/DNA %
Ipriflavone (7-isopropoxy-isoflavone)	8	121	100	121
	10	111	108	103
CH-16693 (7-(-1-cyclohex-2-enyloxy)-isoflavone)	8	110	97	113
	10	131	107	124

The compounds of the general formula (I) may be utilized in the therapy in the form of preparations containing the active ingredient together with inert, non-toxic, pharmaceutically acceptable solid or liquid diluents or carriers.

If desired, the preparations can contain biologically active known substances such as vitamins, amino acids, choline chloride, salts of mineral acids, trace elements etc. As carriers talc, gelatine, calcium carbonate, magnesium stearate, starch, water, polyalkylene glycols etc. may be used. The compositions may be formulated as solid (e.g. tablets, dragées, capsules, suppositories etc.) or liquid (e.g. solution, suspension or emulsion) preparations.

The invention is elucidated in more detail in the following non-limiting examples.

Example 1

10 g of 7-hydroxy-isoflavone, 10 ml of chloroacetone and 8 g of potassium carbonate are stirred in 120 ml of acetone and the mixture is boiled for 5 hours. The reaction mixture is diluted with water, the precipitate is filtered off and recrystallized from acetic acid. 8.5 g of 7-(2-oxopropyl)-isoflavone are obtained, m.p.: 174-175 °C.

7-(2,3-dihydroxy-1-propyloxy)-isoflavone (FL 230), m.p.: 164-165 °C,

7-(3-ethoxycarbonyl-propyloxy)-isoflavone (FL 283), m.p.: 124-125 °C,

7-(2-phenoxyethoxy)-isoflavone (FL 273), m.p.: 195-197 °C,

and

7-(1-ethoxycarbonyl-1-decyloxy)-isoflavone (FL 279), m.p.: 97-99 °C

are prepared in a similar way from 7-hydroxy-isoflavone and the corresponding alkyl halide or substituted alkyl halide.

7-(3-methyl-1-butyloxy)-isoflavone (FL 191), m.p.: 107-108 °C, is prepared from 7-hydroxy-3',4'-dimethoxy-isoflavone by using 3-methyl-1-butylbromid.

7-ethoxy-8-methyl-isoflavone (FL 315), m.p.: 129-130 °C,

7-(carbethoxymethoxy)-8-methyl-isoflavone (FL 316), m.p.: 137-139 °C, and

7-(4-oxo-1-pentyloxy)-isoflavone (FL 501), m.p.: 143-145 °C, are obtained from 7-hydroxy-8-methyl-isoflavone.

Example 2

A mixture of 16 g of 6-n-hexyl-7-hydroxy-isoflavone, 14 ml of isopropylbromide and 70 ml of dimethylformamide are stirred for 4 hours at a temperature of 90 °C in the presence of 16 g of potassium carbonate.

The reaction mixture is poured into 500 ml of water, the product is separated, then recrystallized from 80% aqueous methanol. 15 g of 6-n-hexyl-7-(1-methylethoxy)-

-isoflavone are obtained, m.p. 37-39 °C.

6-n-hexyl-7-ethoxy-isoflavone (FL 319), m.p.: 57-59 °C, and 6-n-hexyl-7--(2-methyl-1-propyloxy)-isoflavone (FL 321), m.p.: 65-67 °C, are prepared in a similar way.

By reacting 6-chloro-7-hydroxy-isoflavones with alkyl halides with the following compounds are prepared:

7-ethoxy-6-chloro-isoflavone (FL 322), m.p.: 162-164 °C,

7-(1-methylethoxy)-6-chloro-isoflavone (FL 323), m.p.: 156-158 °C,

7-(2-methyl-1-propyloxy)-6-chloro-isoflavone (FL 324), m.p.: 170-172 °C,

7-(2-propen-1-yloxy)-isoflavan-4-one (FL 238), m.p.: 76-78 °C and

7-(4-nitro-benzyloxy)-isoflavan-4-one (FL 239), m.p.: 100-102 °C.

Example 3

6.5 g of 7-n-hexadecyloxy-isoflavone are hydrogenated in 1200 ml of acetone in the presence of 3.0 g of 10 % palladium on charcoal catalyst until a hydrogen uptake of 1.2 equimolar amount. The catalyst is filtered off and the solution is evaporated. The residue is recrystallized from a mixture of methanol and acetone to obtain 5.3 g of 7-n-hexadecyloxy-isoflavon-4-one, m.p.: 90-92 °C.

7-ethoxy-5-methyl-isoflavan-4-one (FL 299), m.p.: 97-98 °C, is prepared in a similar way from 7-ethoxy-5-methyl-isoflavone.

7-cyclohexyl-isoflavan-4-one (FL 312), m.p.: 119-120 °C, is prepared from 7-(1-cyclohex-2-enyloxy)-isoflavone (FL 286) by hydrogenation until a hydrogen ptake of 2.2 equimolar amount.

Example 4

A solution of 14 g of 7-isopropyloxy-isoflavone in 160 ml of acetic acid is hydrogenated in the presence of 5% palladium on charcoal catalyst until a hydrogen uptake of 3 equimolar amount. The catalyst is filtered off, the solvent is evaporated and the residue is recrystallized from methanol. 10 g of 7-(1-methylethoxy)-isoflavane (FL199) is obtained, m.p.: 93-95 °C

7-(2-methyl-1-propyloxy)-isoflavane (FL 248), m.p.: 97-99 °C, 7-(n-hexadecyloxy)-isoflavan, m.p.: 90-92 °C, are prepared in a similar way from the corresponding isoflavones.

7-cyclohexyl-isoflavane, m.p.: 90-92 °C, is prepared from 7-(1--cyclohex-2-enyloxy)-isoflavone by hydrogenation until a hydrogen uptake of 4 equimolar amount.

Example 5

2.38 g of 7-hydroxy-isoflavone and 1.94 g of propane sulfone are dissolved in 25 ml of 1% methanolic sodium methylate. The mixture is let stand for 48 hours, then the precipitated product is separated by suction and recrystallized from water to obtain 3.0 g of 7-(3-sulfonyl-1-propyloxy)-isoflavone sodium salt which melts above 350 °C

7-(3-sulfonyl-1-propyloxy)-8-methyl-isoflavone sodium salt (FL 318), m.p.: above 350 °C,

6-chloro-7-(3-sulfonyl-1-propyloxy)-isoflavone (FL 346), m.p.: above 350 °C,

5-methyl-7-(3-sulfo-1-propyloxy)-isoflavone sodium salt (FL 502), m.p.: above 320 °C, and

7-(3-sulfo-1-propyloxy)-2-methyl-isoflavone sodium salt (FL 291), m.p.: above 350 °C

are prepared in a similar way from the corresponding 7-hydroxy-isoflavone derivatives.

Example 6

16.5 g of 7-(3-carbomethoxy-1-proplyoxy)-isoflavone are boiled for 9 hours under reflux in a mixture of 165 ml of glacial acetic acid, 8.5 ml of water and 1.0 ml of concentrated sulfuric acid. The free acid (m.p.: 188-190 °C) precipitates when the mixture is cooled, said acid is removed by suction, dissolved in 300 ml of methanol and the solution is neutralized to pH-8 with 1N sodium methylate solution. The precipitated 7-(3-carboxy-1-propyloxy)-isoflavone sodium salt is separated by suction in an amount of 13.1 g, m.p.: above 320 °C.

7-(1-carboxy-1-propyloxy)-isoflavone, m.p.: 197-200 °C and its sodium salt (FL 282) and

7-(1-carboxy-1-decyloxy)-isoflavone, m.p.: 124-126 °C, and its sodium salt (FL 280)

are prepared in a similar way from the corresponding esters.

Example 7

9 g of 7-isopropyloxy-isoflavone and 3.2 g of paraformaldehyde are stirred for 3 hours at a temperature of 70 °C in a mixture of 80 ml of glacial acetic acid and 40 ml of concentrated hydrochloric acid under continuous introducing of anhydrous gaseous hydrochloric acid. On the next day the solution is partially evaporated, the precipitate is separated by suction and recrystallized from methanol. To the solution of the 7-isopropoxy-8-chloromethyl-isoflavone, m.p.: 123-124 °C, thus obtained with 50 ml of benzene an equivalent amount of

1N sodium methylate is added under boiling. The cooled solution is shaken several times with water and evaporated. The residue is recrystallized from methanol to obtain 7 g of 7-isopropoxy-8-methoxymethyl-isoflavone, m.p.: 92-93 °C.

7-methoxy-8-methoxymethyl-isoflavone (FL 308) is prepared from 7-methoxy-isoflavone in a similar way.

Example 8

To a suspension of 7.5 g of 7-methoxy-8-chloromethyl-isoflavone with 45 ml of glacial acetic acid 3.0 of zinc dust is added within 3 hours. After a further stirring for 8 hours the reaction mixture is diluted with warm water, the precipitate is separated by suction and recrystallized from ethanol. 5.1 g of 7-methoxy-8-methyl-isoflavone are obtained, m.p.: 133-135 °C.

Example 9

36.2 g of 2-hydroxy-4-(3-phenoxy-1-propyloxy)-phenylbenzyl-ketone, 22 g of ethyl orthoformiate and 5 g of morpholine are boiled in 200 ml of dimethyl formamide for 8 hours. The ethanol formed during the reaction is removed through a fractionating attachment, then a great part of the solvent is evaporated in vacuo and the residue is diluted with diluted aqueous hydrochloric acid. The raw product is filtered off and recrystallized from acetone to obtain 32 g of 7-(3-phenoxy-1-propyloxy)-isoflavone (FL 230), m.p.: 123-125 °C.

Example 10

9.8 g of 7-(3-chloro-1-propyloxy)-isoflavone are boiled with 4.1 ml of piperidine in 55 ml of 2-butanone in the presence of 5.5 g of potassium carbonate and 0.5 g of potassium iodide for 14 hours. The inorganic salts are filtered off while hot and after cooling the precipitated product is separated by suction and recrystallized from methanol. 7-[3-(1-piperidine)-propyloxy]-isoflavone (FL 118) is obtained in an amount of 6.0 g, m.p.: 138-139 °C.

7-[3-(1-morpholinyl)-propyloxy]-isoflavone (FL 117) is obtained in a similar way, m.p.: 162-163 °C.

Example 11

18.5 g of 7-(10-ethoxycarbonyl-1-decyloxy)-isoflavone are boiled in a mixture of 180 ml of glacial acetic acid, 10 ml of water and 3 ml of concentrated sulfuric acid for 4 hours. The next day the precipitated 7-(10-carboxy-1-decyloxy)-isoflavone, m.p.: 118-120 °C, is separated by suction, dissolved in a 4:1 mixture of acetone and methanol and the solution is adjusted to pH 8 by the aid of 10%

sodium hydroxyde. The precipitated salt is separated by suction and washed with the solvent mixture. 7-(10-carboxy-1-decyloxy)-isoflavone sodium salt (FL 295) is obtained in an amount of 10.6 g, which melts above 360 °C.

7-(5-carboxy-1-pentyloxy)-isoflavone, m.p.: 146-148 °C, is obtained from 7-(5-carbethoxy-1-pentyloxy)-isoflavone in a similar way and then the corresponding sodium salt (FL 302) which melts above 360 °C.

Example 12

3.0 g of 7-methoxy-isoflavone are dissolved in 30 ml of chloroform and then 2.0 g of sulfurylchloride are added to the solution. The mixture is boiled for an hour, evaporated, then the residue is recrystallized from a 1:1 mixture of chloroform and ethanol. 8-chloro-7-methoxy-isoflavone (FL 501) is obtained in an amount of 22.5 g, m.p.: 181-182 °C.

In a similar way 7-ethoxy-isoflavone, m.p.: 144-145 °C, is prepared from 7-ethoxy-isoflavone, 8-chloro-7-(2-propyloxy)-isoflavone, m.p.: 167-169 °C, from 7-(2-propyloxy)-isoflavone and 8-chloro-2-methyl-7-methoxy-isoflavone (FL 517), m.p.: 176-178 °C, from 2-methyl-7-methoxy-isoflavone.

Example 13

2.0 g of 7-(carbethoxymethoxy)-isoflavone are dissolved in 10 ml of diethylamino ethanol, 2.0 g of potassium carbonate are added to the solution and the mixture is boiled for 5 hours under stirring, then poured into a mixture of ice and 2% hydrochloric acid. The product is separated by suction and recrystallized from a mixture of methanol and acetone. 7-(N,N-diethylaminoethoxy--carbonylmethoxy)-isoflavone (FL 105) is obtained in an amount of 1.5 g, m.p.: 227-228 °C.

7-(N,N-diethylaminoethoxy-carbonylmethoxy)-2-methyl-isoflavone (FL 104), m.p.: 190-192 °C, is prepared in a similar way from 7-(carbethoxymethoxy)-2-methyl-isoflavone.

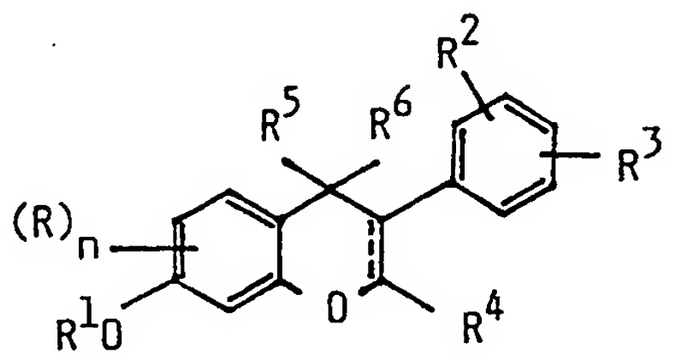
Example 14

16.0 g of 8-chloromethyl-7-methoxy-isoflavone and 11.4 g of anhydrous sodium acetate are boiled in 80 ml of acetic anhydride for 4 hours. The reaction mixture is poured onto water, the precipitated product is filtered off and recrystallized from acetic acid. 8-acetoxymethyl-7-methoxy-isoflavone (FL 509) is obtained in an amount of 11.7 g, m.p.: 195-197 °C.

8-acetoxymethyl-7-(2-propyloxy)-isoflavone (FL 521), m.p.: 107-109 °C, is prepared from 8-chloromethyl-7-(2-propyloxy)-isoflavone in a similar way.

Claims:

1. Process for the preparation of compounds of the general formula



(I),

and salts thereof, wherein

if n is 0, R^5 and R^6 together stand for an oxo group and the dotted line means a double bond,

R^1 represents C_{1-18}alkyl substituted by alkylcarbonyl, carboxy, sulfonic acid, hydroxy, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N\text{-}(CH_2)_mCO(CH_2)_p$- or by $(C_{1-4}alkyl)_2N\text{-}(CH_2)_mOCO(CH_2)_p$- group; or stands for C_{3-6}cycloalkyl or cycloalkenyl; or

if n is 1, R^5 and R^6 together stand for an oxo group and the dotted line means a double bond,

R^1 represents C_{1-18}alkyl optionally substituted by alkyl-carbonyl, alkoxycarbonyl, carboxy, sulfonic acid, hydroxy, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N\text{-}(CH_2)_mCO(CH_2)_p$- group; or stands for C_{3-6}-cycloalkyl or cycloalkenyl or C_{2-6}alkenyl; or

if n is 0 or 1, R^5 and R^6 together stand for an oxo group or stand separately for hydrogen and the dotted line does not mean a chemical bond,

R^1 represents C_{1-18}alkyl optionally substituted by alkyl-carbonyl, alkoxycarbonyl, carboxy, sulfonic acid, hydroxy, alkoxy, phenyl optionally substituted by a halo atom, phenoxy, piperidino, morpholino or piridino or by a $(C_{1-4}alkyl)_2N\text{-}(CH_2)_mCO(CH_2)_p$- group; or stands for C_{3-6}-cycloalkyl or C_{2-6}alkenyl; or

R stands for C_{1-8}alkyl, halogen, C_{1-4}alkoxymethyl, C_{2-5}-acyloxymethyl, or hydroxymethyl;

R^4 stands for hydrogen or C_{1-4}alkyl;

R^2 and R^3 stand for hydrogen or C_{1-6}alkoxy;

R^5 and R^6 together stand for an oxo group or separately stand for hydrogen;

the dotted line means a double bond being optionally present;

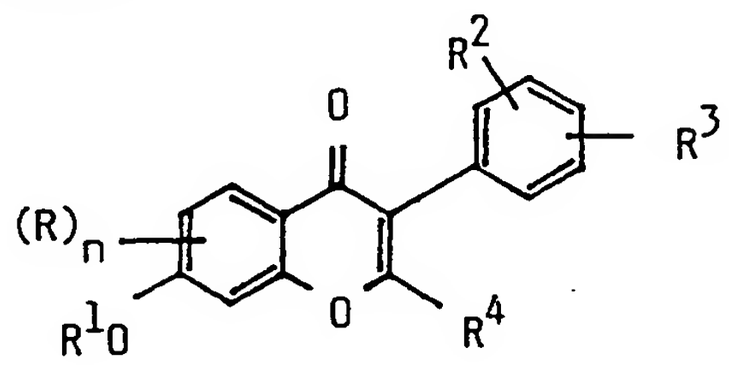
n is 0 or 1;

m is an integer from 1 to 4; and

p is an integer from 1 to 4.

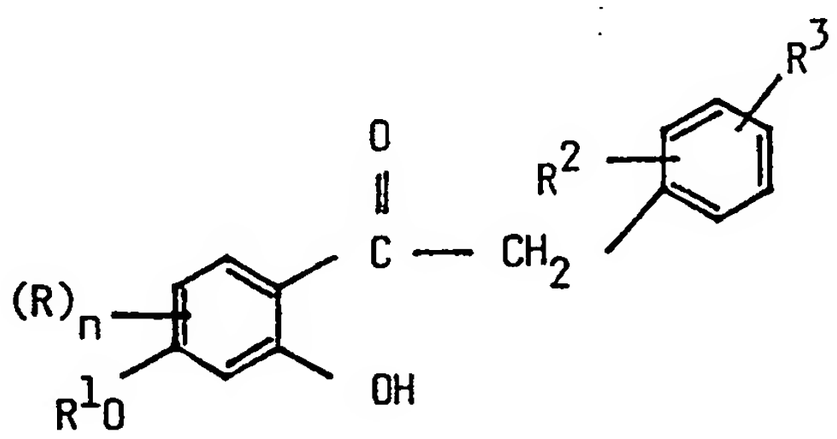
characterized in that

1) for the preparation of compounds of the general formula



(IA),

wherein R, n, R^1, R^2 and R^3 are as defined in the preamble, forming a narrower group of the compounds of the general formula (I), ketones of the general formula



(III),

wherein R, n, R^1, R^2 and R^3 are as defined for the general formula (I), are reacted

a) with alkyl orthoformate in the presence of a basic catalyst, or

b) with hydrogen cyanide and/or cyanic salts in the presence of hydrohalogenic acid; or

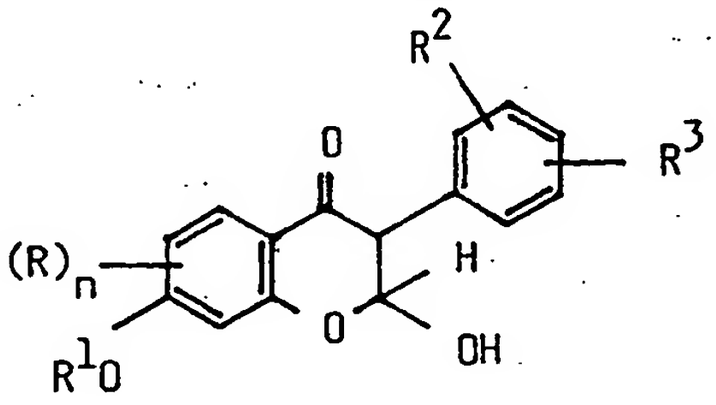
c) with alkyl formiate in the presence of an alkali metal; or

d) with alkyloxalyl halide, and the isoflavone ester thus obtained is, if desired, saponified and/or decarboxylated; or

e) with organic carboxylic anhydride; or

f) with N,N-dialkyl acid amide in the presence of phosphorous chloride; or

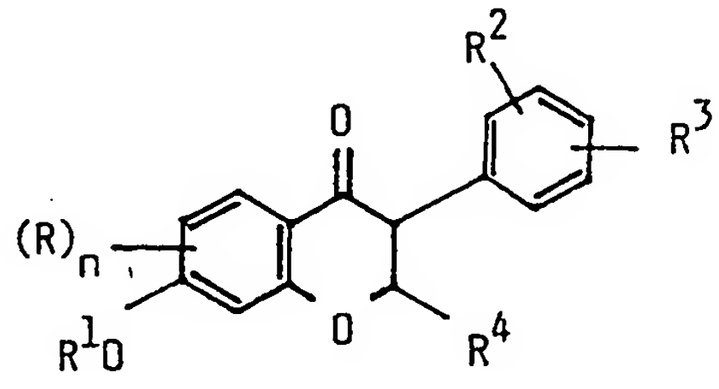
g) 2-hydroxy-isoflavanone derivatives of the general formula



(IV),

are dehydrated, or

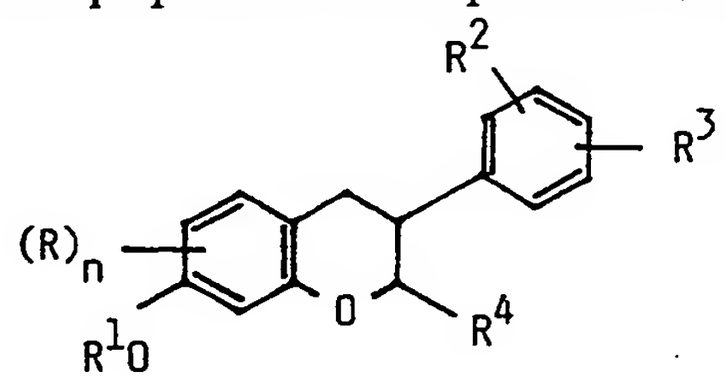
2) for the preparation of compounds of the general formula



(IB),

wherein R, n, R^1, R^2 R^3 and R^4 are as defined in the preamble, forming a narrower group of the compounds of the general formula (I), compounds of the general formula (IA), wherein R, n, R^1, R^2 R^3 and R^4 are as defined in the preamble, are subjected to reduction, or

3) for the preparation of compounds of the general formula



(IC),

wherein R, n, R^1, R^2 R^3 and R^4 are as defined in the preamble, forming a narrower group of the compounds of the general formula (I), compounds of the general formula (IB), wherein R, n, R^1, R^2 R^3 and R^4 are as defined in the preamble, are reduced by catalytic hydrogenation,

and, if desired, an R^1 is converted into another R^1 group within the definitions of the preamble,

or an R group is formed in a compound of the general formula (I) containing a hydrogen atom in the place of R,

and, if desired, a compound of the general formula (I) thus obtained is converted into its salt or is set free from its salt.

2. Processes according to variants a) to f) of claim 1, characterized by using 2-hydroxy-4-alkoxyphenylbenzyl-ketone as a starting material of the general formula (III).

3. A process as claimed in claim 2, characterized by using 2-hydroxy-4-isopropoxyphenylbenzyl-ketone as starting material of the general formula (III).

4. A process as claimed in variant a) of claim 1, characterized by using piperidine, morpholine or pyrrolidine as basic catalyst.

5. A process as claimed in variant b9 of claim 1, characterized by carrying out the reaction in an aprotic solvent, preferably in dialkyl ether or another dialkyl ether.

6. A process as claimed in claim 5, characterized by carrying out the reaction in the presence of Lewis acids, preferably in the presence of zinc chloride.

7. A process as claimed in variant c) of claim 1, characterized by using sodium as an alkali metal.

8. A process as claimed in variant e) of claim 1, characterized by using acetic anhydride, propionic anhydride or benzoic anhydride as organic acid anhydride.

9. A process as claimed in claim 8, characterized by carrying out the reaction in the presence of a basic catalyst, preferably in the presence of the alkali salt of the acid component of the acid anhydride or a tertiary amine.

10. A process as claimed in variant f) of claim 1, characterized by using dimethylformamide or dimethylacetamide as N,N-dialkyl acid amide.

11. A process as claimed in variant g) of claim 1, characterized by carrying out the dehydration in an acidic medium.

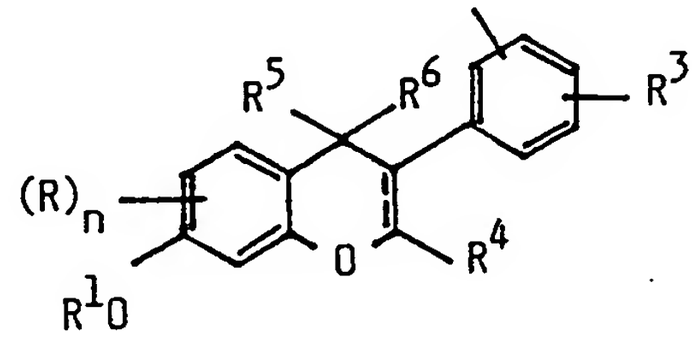
12. A process as claimed in claim 1, characterized by introducing the R^1 group by alkylating the compounds of the general formula (I) containing a hydrogen atom in the place of R^1 with alkyl halides, alkyl sulfates, alkyl sulfonic lactones, olefines or epoxydes.

13. A process as claimed in variant 2) of claim 1, characterized by carrying out the reduction by catalytic hydrogenation or by using metal hydrides.

14. A process as claimed in variant 3) of claim 1, characterized by using as catalyst nickel or a noble metal catalyst.

15. A process for the preparation of pharmaceutical compositions, characterized by admixing a compound of the general formula (I) wherein R^1, R, R^2, R^3 R^4, R^5, R^6, n, m, p and the dotted line are as defined in claim 1, or a salts thereof, with inert, non-toxic, pharmaceutically acceptable solid or liquid diluents or carriers and other excipients and formulating pharmaceutical compositions.

16. Compounds of the general formula



(I),

and salts thereof.

17. Pharmaceutical compositions containing compounds of the general formula (I).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 94/00028

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 311/36; A 61 K 31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 311/36; A 61 K 31/35

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DARC, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A, 91/15 483 (CHINOIN) 17 October 1991 (17.10.91), claims 1-4.	1,15-17
A	EP, A, 136 569 (TAKEDA CHEMICAL INDUSTRIES) 10 April 1985 (10.04.85), claims 1-3.	1,15-17
A	Chemical Abstracts, Vol. 108, no. 1, issued 1988, January 04 (Columbus, Ohio, USA) WATANABE, S. et al. "Use of isoflavone derivatives as immunosuppressants." page 53, column 2, abstract no. 622c & Jpn. Kokai Tokkyo Koho JP 62 106 016 [87 106 016].	1,15-17
A	Chemical Abstracts, Vol. 104, no. 17, issued 1986, April 28 (Columbus, Ohio, USA) MATSUDA, Y. et al. "Isoflavone derivatives" page 548, column 2, abstract no. 147 153b, & Jpn. Kokai Tokkyo Koho JP 60 199 396 [85 199 396].	1,15-17

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 December 1994 (02.12.94)	12 December 1994 (12.12.94)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Brus e.h. Telephone No. 1/5337058/32

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 94/00028

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol. 87, no. 3, issued 1977, July 18 (Columbus, Ohio, USA) NORO, T. et al. "Syntheses of isoflavone derivatives. II. Synthesis of 6-hydroxy-2'-methoxy-5'-nitroisoflavone" page 623, column 2, abstract no. 22 970q & Yakugaku Zasshi 1977, 97 (2), 215-17.	1,15-17

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU 94/00028

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO 9115483		keine - none - rien	
EP 136569		EP A2 136569	10-04-85
		EP A3 136569	07-01-87
		HU A2 36111	28-08-85
		JP A2 60054379	28-03-85